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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 7/00 | A2

(11) International Publication Number: **WO 98/24807**

(43) International Publication Date: 11 June 1998 (11.06.98)

(21) International Application Number: PCT/US97/22251

(22) International Filing Date: 4 December 1997 (04.12.97)

(30) Priority Data:

60/032,358	4 December 1996 (04.12.96)	US
08/760,672	4 December 1996 (04.12.96)	US
08/855,204	13 May 1997 (13.05.97)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: SOMATOSTATIN ANTAGONISTS

(57) Abstract

The invention features somatostatin antagonists having a D-amino acid at the second residue.

BNSDOCID: <WO___9824807A2_I_>

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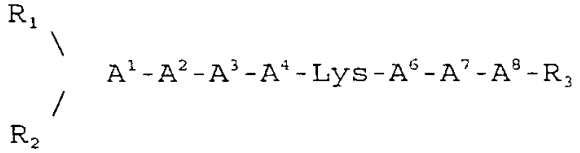
SOMATOSTATIN ANTAGONISTS

Background of the Invention

Native somatostatin is comprised of both a 14-amino acid isoform (somatostatin-14) and a 28-amino acid isoform (somatostatin-28). Heiman, et al., Neuroendocrinology, 45:429-436 (1987). Because of the short half-life of the native somatostatin, various somatostatin analogs have been developed, e.g., for the treatment of acromegaly. Raynor, et al., Molecular Pharmacol. 43:838 (1993). Five distinct somatostatin receptors have been identified and characterized. Hoyer, et al., Naunyn-Schmiedeberg's Arch. Pharmacol., 350:441 (1994). Somatostatin produces a variety of effects, including modulation of hormone release, e.g., growth hormone, glucagon, insulin, amylin, and neurotransmitter release. Some of these effects have been associated with its binding to a specific somatostatin receptor. For example, the inhibition of growth hormone has been attributed to the somatostatin type-2 receptor ("SSTR-2") (Raynor, et al., Molecular Pharmacol. 43:838 (1993); Lloyd, et al., Am. J. Physiol. 268:G102 (1995)) while the inhibition of insulin has been attributed to the somatostatin type-5 receptor ("SSTR-5") (Coy, et al. 197:366371 (1993)). The following invention relates to a novel class of somatostatin analogs which are antagonists to somatostatin receptors.

Summary of the Invention

The invention features a compound of the formula:



wherein

A^1 is a D- or L-isomer of an aromatic amino acid, or is deleted;

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A^2 is a D-isomer selected from the group consisting of Cys, Pen, an aromatic amino acid, or an aliphatic amino acid;

A^3 is an aromatic amino acid;

A^4 is Trp or D-Trp;

A^6 is Thr, Thr(Bzl), Gly, Ser, an Eaa, or an aliphatic amino acid;

A^7 is Cys, Pen, or an aromatjkic or an aliphatic amino acid;

A^8 is a D- or L-isomer selected from the group consisting of Thr, Ser, an aromatic amino acid, or an aliphatic amino acid;

each of R^1, and R^2, is, independently, H or substituted (e.g., one to four times) or unsubstituted lower alkyl, aryl, aryl lower alkyl, heterocycle, heterocycle lower alkyl, E_1SO_2 or E_1CO (where E_1 is aryl, aryl lower alkyl, heterocycle, or heterocycle lower alkyl), where said substituent is halo, lower alkyl, hydroxy, halo lower alkyl, or hydroxy lower alkyl; and

R_3 is OH, NH_2, C_{1-12} alkoxy, or NH-Y-CH_2-Z, wherein Y is a C_{1-12} hydrocarbon moiety and Z is H, OH, CO_2H, or $CONH_2$, or R_3, together with the carbonyl group of A^8 attached thereto, are reduced to form H, lower alkyl, or hydroxy lower alkyl; provided if A^2 is D-Cys or D-Pen, and A^7 is Cys or Pen, then a disulfide bond links the sidechains of A^2 and A^7 , and if A^1 is D-Phe or p-NO_2-Phe; A^2 is D-Cys; A^3 is Phe or Tyr; A^6 is Thr or Val; and A^7 is CYS; then A^8 is β-Nal.

In one embodiment, A^2 is D-Cys, A^7 is Cys, and A^4 is D-Trp. In a further embodiment, A^1 is an L-aromatic amino acid.

In still a further embodiment, A^1 and A^3, independently, is β-_Nal, o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2,), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5,-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl,

Tyr(I), Bta, Bip, Npa, or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F^5-Phe, p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2) , o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal. In yet still another embodiment, A^1 is β-Nal, Npa, Igl, Phe, p-F-Phe, Trp, p-Cl-Phe, or p-CN-Phe; A^3 is Tyr, Tyr(I), or Pal; A^6 is Val, Tle, Nle, Ile, or Leu; A^8 is p-F-Phe, β-Nal, Tyr, Dip, pCl-Phe, Igl, or p-CN-Phe; R_1 is H, CH_3CO, 4-(2-hydroxyethyl)-1piperazinylacetyl, or 4-(2-hydroxyethyl)-1piperizineethanesulfonyl; R_2 is H; and R_3 is NH_2.

In another further embodiment, A^1 is a D-aromatic amino acid. In still another further embodiment, A^1 is D-β-Nal, D-o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, D-Trp, D-Dip, D-2-Pal, D-Tyr(Bzl), D-His, D-Igl, D-Tyr(I), D-Bta, D-Bip, D-Npa, or D-Pal; A^3 is β-Nal, o-X-Phe (where X is H,OH,CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2,), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F^5-Phe, p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Tyr(Bzl), Igl, or β-Nal.

In yet still a further embodiment, A^1 is D-β-Nal, D-Npa, D-Igl, D-Phe, D-p-F-Phe, D-Trp, D-p-Cl-Phe, or D-p-CN-Phe; A^3 is Tyr, Tyr(I), or Pal; A^6 is Val, Tle, Nle, Ile, or Leu; A^8 is p-F-Phe, β-Nal, Tyr, Dip, p-Cl-Phe, Igl, or p-CN-

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Phe; R^1 is H, CH_3CO, 4-(2-hydroxyethyl)-1-piperazinylacetyl, or 4-(2-hydroxyethyl)-lpiperizineethanesulfonyl; R_2 is H; and R_3 . NH_2.

In still another further embodiment, A^1 is deleted, R^1 is substituted or unsubstituted E_1CO, and R_2 is H. In still a further embodiment, R_1 is substituted or unsubstituted E_1CO (where E_1 is phenyl, β-naphthylmethyl, β-pyridinylmethyl, or 3-indolylmethyl); A^3 is β-Nal, o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-X-Phe (where X is H, OH, CH_3,, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal.

In yet still a further embodiment, R^1 is E_1CO (where E_1 is 4-hydroxy-phenyl, β-naphthylmethyl, or phenyl); A^3 is Tyr, Tyr(I), or Pal; A^6 is Val, Tle, Nle, Ile, or Leu; A^8 is p-F-Phe, β-Nal, Tyr, Dip, p-Cl-Phe, Igl, or p-CN-Phe; R^3 is NH_2.

In yet still a further embodiment, R^3, together with the carbonyl group of A^8 attached thereto, are reduced to form H, lower alkyl, or hydroxy lower alkyl. In still another further embodiment, A^1 is the D- or L-isomer of β-Nal, o-X-Phe (where X is H, OH, CH3, halo, OCH3, NH2, CN, or N02), p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^3 is β-Nal, o-X-Phe (where X is H, OH, CH^3, halo, OCH_3, NH_2, CN, or NO_2) , p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe,

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Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl),Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal.

In yet still another further embodiment, A^1 is the D- or Lisomer of β-Nal, Phe, p-F-Phe, Trp, p-Cl-Phe, or p-CN-Phe; A^3 is Tyr, Tyr(I), or Pal; A^6 is Val, Tle, Nle, Ile, or Leu; A^3 is p-F-Phe, β-Nal, Tyr, Dip, p-Cl-Phe, Igl, or p-CN-Phe; R_1 is H, CH_3CO, 4-(2-hydroxyethyl)-1-piperazinylacetyl, or 4-(2-hydroxyethyl)-1-piperizineethanesulfonyl; R_2 is H, and R_3, together with the carboxy group of A^8 attached thereto, are reduced to form H or CH_3OH.

In another embodiment, A^2 is a D-aromatic amino acid or a D-aliphatic amino acid, A^7 is an aromatic amino acid or an aliphatic amino acid, and A^4 is D-Trp. In a further embodiment, A^1 is an L- amino acid and A^2 is a D-aromatic amino acid. In still a further embodiment, A^1, A^3, and A^7 independently, is β-Nal, o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^2 is D-β-Nal, D-o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-F_5-Phe, D-Trp, D-Dip, D-2-Pal, D-Tyr(Bzl), D-His, D-Igl, D-Tyr(I), D-Bta, D-Bip, D-Npa, or D-Pal; A^6 Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2) , o-X-Phe (where X is H, OH, CH_3, halo,

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OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Tyr(Bzl) , Igl, or β-Nal.

In yet still a further embodiment, A^1 is β-Nal or Phe, A^2 is D-Cpa or D-Phe; A^3 is Phe or Tyr; A^6 is Abu, Thr, or Val; A^7 is Phe; and A^8 is Thr; R_1 is H, CH_3CO, 4-(2-hydroxyethyl)-1-piperazinylacetyl, or 4-(2-hydroxyethyl)-1-piperizineethanesulfonyl; R_2 is H; and R_3 is NH_2.

In another further embodiment, A^1 is a D-amino acid and A^2 is a D-aromatic amino acid.

In still a further embodiment, A^1 and A^2, independently, is D-β-Nal, D-o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-p-X-Phe (where X is H, OH, CH_3, halo, OCH_3,, NH_2, CN, or NO_2), D-m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-F_5-Phe, D-Trp, D-Dip, D-2-Pal, D-Tyr(Bzl), D-His, D-Igl, D-Tyr(I), D-Bta, D-Bip, D-Npa, or D-Pal; A^3 and A^7, independently, is β-Nal, o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, His, Igl, Tyr(I), Bta, Bip, Npa, Tyr(Bzl), or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F^5-Phe, p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal.

In yet still a further embodiment, A^1 is D-β-Nal or D-Phe; A^2 is D-Cpa or D-Phe; A^3 is Phe or Tyr; A^6 is Thr or Val; A^7 is Phe; and A^8 is Thr; R_1 is H, CH_3CO, 4-(2-hydroxyethyl)-1-piperazinylacetyl, or 4-(2-hydroxyethyl)-1-piperizineethanesulfonyl; R_2 is H; and R_3 is NH_2.

Examples of compounds of the present invention include the following:

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 2);

(H) (CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2, (Analog No. 5);

(H)-(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)-(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 3)

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)-(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)-(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 4);

(H) (CH_3CO)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(CH_3CO)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-

Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys--Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(CH_3CO)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys--Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe- D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-:L-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2

(Analog No. 6);

(H)(CH_3CO)-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

H_2-Phe-D-Pen-Tyr-D-Trp-Lys-Val-Pen-β-Nal-NH_2; or

H_2-Phe-D-Pen-Pal-D-Trp-Lys-Thr-Pen-Thr-NH_2;

H_2-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-Dip-NH_2

(Analog No. 10);

H_2-F_5-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-F_5-Phe-NH_2 (Analog No. 11);

H_2-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 13);

H_2-m-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-m-F-Phe-NH_2 (Analog No. 14);

H_2-o-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-o-F-Phe-NH_2 (Analog No. 15);

H_2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-p-F-Phe-NH_2 (Analog No. 12);

H_2-F_5-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-F_5-Phe-NH_2 (Analog No. 16);

H_2-F_5-Phe-D-Cys-2-Pal-D-Trp-Lys-Val-Cys-F_5-Phe-NH_2 (Analog No. 17);

H_2-β-Nal-D-Cys-His-D-Trp-Lys-Val-Cys-D-Dip-NH_2 (Analog No. 19);

H_2-Dip-D-Cys-His-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 20);

H_2-Dip-D-Cys-His-D-Trp-Lys-Val-Cys-Dip-NH_2 (Analog No. 21);

H_2-β-Nal-D-Cys-His-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 22);

H_2-Trp-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-β-Nal-NH_2 (Analog No. 24);

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-β-Nal-NH_2 (Analog No. 25);

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-p-F-Phe-NH_2 (Analog No. 28);

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2 (Analog No. 29);

H_2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 30);

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Nle-Cys-β-Nal-NH_2, (Analog No. 31);

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Ile-Cys-β-Nal-NH_2,

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(Analog No. 32);

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Gly-Cys-β-Nal-NH_2

(Analog No. 33);

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Ala-Cys-β-Nal-NH_2

(Analog No. 34);

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Leu-Cys-β-Nal-NH_2

(Analog No. 35);

H_2-Bip-D-Cys-Tyr-D-Trp-Lys-Ile-Cys-Bip-NH_2

(Analog No. 36);

H_2-p-F-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-p-F-Phe-NH_2

(Analog No. 38);

H_2-Npa-D-cys-Pal-D-Trp-Lys-Val-Cys-Tyr-NH_2

(Analog No. 39);

H_2-m-F-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-m-F-Phe-NH_2

(Analog No. 40);

H_2-o-F-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-o-F-Phe-NH_2

(Analog No. 41);

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Dip-NH_2

(Analog No. 42);

H_2-Cpa-D-Cys-Pal-D-Trp-Lys-Val-Cys-Cpa-NH_2

(Analog No. 43);

H_2-Igl-D-Cys-Pal-D-Trp-Lys-Val-Cys-Igl-NH_2

(Analog No. 44);

H_2-P-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-Dip-NH_2

(Analog No. 45);

H_2-β-Nal-D-Cys-3-I-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2

(Analog No. 46);

H_2-p-CN-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-p-CN-Phe-NH_2

(Analog No. 47);

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-Dip-NH_2

(Analog No. 48);

H_2-β-Nal-D-Cys-Bta-D-Trp-Lys-Val-Cys-p-Nal-NH-,

(Analog No. 49);

H_2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2

(Analog No. 50);

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H_2-Bpa-D-Cys-Pal-D-Trp-Lys-Val-Cys-Bpa-NH_2 (Analog No. 52);

H_2-Iph-D-Cys-Pal-D-Trp-Lys-Val-Cys-Iph-NH_2 (Analog No. 53);

H_2-Trp-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2 (Analog No. 54);

H_2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 55);

H_2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2 (Analog No. 56);

H_2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-p-Cl-Phe-NH_2 (Analog No. 57);

H_2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Cha-Cys-p-Cl-Phe-NH_2;

H_2-p-Cl-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH_2;

H_2-p-Cl-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-P-Cl-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;

H_2-p-F-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-p-F-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

(H)(CH_3CO)-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-p-NO_2-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Tyr-NH_2;

H_2-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

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H_2,-β-Nal-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-β-Nal-NH_2;

(H)(4-2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-NH_2;

H_2-D-Phe-D-Pen-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 9);

H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-D-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-D-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-β-Nal-NH_2 (Analog No. 26);

H_2-D-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-p-F-Phe-NH_2 (Analog No. 27);

H_2-D-Bip-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 37);

H_2-D-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (Analog No. 18);

H_2-D-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2 (Analog No. 51);

H_2-D-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-p-Cl-Phe-NH_2 (Analog No. 7);

p-NO_2-D-Phe-D-Cys-Pal-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-NH_2;

p-NO_2-D-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Val-Cys-Tyr(Bzl)-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-D-Phe-D-Cys-Pal-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-D-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Val-Cys-Tyr(Bzl)-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-β--

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Nal-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(3-[p-hydroxyphenyl])-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

(H)(3-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

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(H)(3-phenylylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2

(H)(3-phenylylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-

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hydroxymethyl)-3-hydroxy)propylamide;

(H) (CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R, 3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO) Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R, 3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H(CH_3CO)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H) (CH_3CO) Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R, 3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-

Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H) (CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

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(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H) (CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H) (CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H) (CH_3CO)Phe-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H) (CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)

Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H) (CH_3CO) Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H_2-Phe-D-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-Phe-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2 (Analog No.

(H) (CH_3CO)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-β-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H) (CH_3CO)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2,-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(CH_3CO)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

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(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D--Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β--Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H_2-β-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H) (CH_3CO)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H_2-P-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2;

(H)(CH_3CO)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2; or

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2;

H_2-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2 (Analog No. 23);

H_2-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-D-β-Nal-D-Cpa-Phe-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-D-β-Nal-D-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H_2-D-Phe-D-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-D-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2 (Analog No. 8); or

H_2-D-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2; or a pharmaceutically acceptable salt thereof.

With the exception of the N-terminal amino acid, all abbreviations (e.g., Ala or A_2) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is a side chain of an amino acid (e.g., CH_3 for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of =N-CH(R)-CO-, wherein R is a side chain of an amino acid. Pen, β-Ala, Gaba, Nle, Nva, Pal, F_5-Phe, 2,4-dichloro-Phe, Cpa, β-Nal, β-1-Nal, Abu, Dip, 2-Pal, Bip, Npa, Igl, Bta, Tle, Bpa, Iph, Cha,

Thr(Bzl), Tyr(Bzl), and Aib are respective abbreviations of the following α-amino acids: penicillamine, 3-aminopropionic acid, 4-aminobutyric acid, norleucine, norvaline, β-[3-pyridyl]-alanine, β-[2,3,4,5,6-pentafluorophenyl]-alanine,β-[2,4-dichlorophenyl]-alanine, β[4-chlorophenyll-alanine, β-[2-napthyll-alanine, β-[1-naphthyl]-alanine; 2-aminobutyric acid, 3,3'-diphenylalanine, β-[2-pyridyl]-alanine, 4,4'-biphenylalanine, p-NO_2phenylalanine, 2-indanylglycine, 3-benzothienylalanine, α-[t-butyl]-glycine, 4-bromo-phenylalanine, 4-iodo-phenylalanine, β-(cyclohexyl)-alanine, O-benzyl-threonine, O-benzyl-tyrosine, and 2-aminoisobutyric acid. Tyr(I) refers to an iodinated tyrosine residue (e.g., 3-I-Tyr, 5-I-Tyr, 3,5-I-Tyr) wherein the iodine may be a radioactive isotope, e.g., I_{125}, I_{127}, or I_{131}. An aliphic amino acid is an α-amino acid having one or two side chains which, independently, are hydrocarbons, e.g., a straight or branched chain of 1-6 carbons. Examples of aliphatic amino acids include Ala, Aib, Val, Leu, Tle, Ile, Nle, Nva, or Abu. An aromatic amino acid is an α-amino acid the side chain of which has a neutral (e.g., not acidic or basic) aromatic substituent, e.g., a substituted or unsubstituted phenyl, naphthyl, or aromatic heterocycle group (e.g., pyridyl or indolyl). Examples of aromatic amino acids include Phe, p-X-Phe (where X is a halo (e.g., F, Cl, Br, or I), OH, OCH_3, CH_3, or NO_2), o-X-Phe (where X is a halo, OH, OCH_3, CH_3, or NO_2), m-X-Phe (where X is a halo, OH, OCH_3, CH_3, or NO_2), His, Pal, Trp, β-Nal, 2,4-dichloro-Phe, Tyr(I), β-[3,4,5-trifluorophenyl]-alanine, Bta, β-[3-cyanophenyl]alanine, β-[4-cyanophenyl]-alanine, β-[3,4-difluorophenyl]-alanine, β-[3,5-difluorophenyl]-alanine, β-[2-fluorophenyl]alanine, β-[4-thiazolyl]-alanine, Bip, Dip, Npa, Igl, Bpa, Iph, homophenylalanine, 2-Pal, β-[4-pyridyl]-alanine, β-[4-thiazolyl]-alanine, β-[2-thiazolyl]-alanine, para-(CF_3)-

phenylalanine, and F_5,-Phe. What is meant by an "Eaa" is an amino acid of the formula -NH- [CH(R)$_n$,-CO- (where n is 2-6 and R is H, lower alkyl, or hydroxy lower alkyl). Examples of an Eaa include β-Ala and Gaba.

As used herein, "lower alkyl", is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having 1-6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, sec-butyl, and the like.

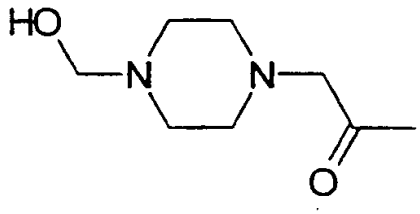
As used herein, "aryl", is intended to include any stable monocyclic, bicyclic, or tricyclic carbon ring(s) of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include phenyl, naphthyl, anthracenyl, biphenyl, tetrahydronaphthyl, indanyl, phenanthrenyl, and the like.

The term "heterocyclyl", as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl,

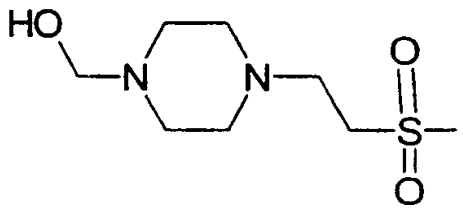
isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, and the like.

The term "substituted" is meant to include the recited chemical group (e.g., lower alkyl, heterocycle, aryl, cycloalkyl, etc.) substituted with one to four of the recited substituents (e.g., halo, hydroxy, lower alkyl, etc.). The substituent may be attached to any atom in the chemical group.

The structure of 4-(2-hydroxyethyl)]-1--piperazinylacetyl and 4-(2-hydroxyethyl)]-1-piperizineethanesulfonyl are, respectively, as follows:



and



The compounds of this invention can be provided in the form of pharmaceutically acceptable salts. Acceptable salts include, but are not limited to, acid addition salts of inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or organic acids such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methanesulfonate, p-toluenesulfonate, pamoate, salicylate, oxalate, and stearate. Also within the scope of the present invention, where applicable, are salts formed from bases such as

sodium or potassium hydroxide. For further examples of pharmaceutically acceptable salts see, "Pharmaceutical Salts," J. Pharm. Sci. 66:1 (1977).

Where the amino acid residue is optically active, it is the L-isomer that is intended unless otherwise specified. In the formulae set forth herein, the disulfide bond between the thiol group on the side chain of residue A_2 (e.g., Cys, Pen, D-Cys, or D-Pen) and the thiol group on the side chain of residue A_7 (e.g., Cys or Pen) is not shown.

The peptides of the invention can be used to promote the release of growth hormone or insulin in a subject (e.g., a mammal such as a human patient). Thus, the peptides are useful in the treatment of physiological conditions in which the promotion of the release of growth hormone or insulin is of benefit. The peptides of the invention can also be used in enhancing wound healing or promoting angiogenesis. Also, peptides of the invention having a Tyr(1) residue can be used to image cells containing somatostatin receptors. Such peptides of the invention can be used either *in vivo* to detect cells having somatostatin receptors (e.g., cancer cells) or *in vitro* as a radioligand in a somatostatin receptor binding assay. The peptide of the invention can also be used as vectors to target cells with radioactive isotopes.

A therapeutically effective amount of a peptide of this invention and a pharmaceutically acceptable carrier substance (e.g., magnesium carbonate, lactose, or a phospholipid with which the therapeutic compound can form a micelle) together form a therapeutic composition (e.g., a pill, tablet, capsule, or liquid) for administration (e.g., orally, intravenously, transdermally, pulmonarily, vaginally, subcutaneously, nasally, iontophoretically, or by intratracheally) to a subject in need of the peptide. The pill, tablet, or capsule can be coated with a substance

capable of protecting the composition from the gastric acid or intestinal enzymes in the subject's stomach for a period of time sufficient to allow the composition to pass undigested into the subject's small intestine. The therapeutic composition can also be in the form of a biodegradable or nonbiodegradable sustained release formulation for subcutaneous or intramuscular administration. See, e.g., U.S. Patents 3,773,919 and 4,767,628 and PCT Application No. WO 94/00148. Continuous administration can also be obtained using an implantable or external pump (e.g., INFUSAID TM pump) to administer the therapeutic composition.

The dose of a peptide of the present invention for treating the above-mentioned diseases or disorders varies depending upon the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such an amount of the peptide as determined by the attending physician or veterinarian is referred to herein as a "therapeutically effective amount".

Also contemplated within the scope of this invention is a peptide covered by the above generic formula for both use in treating diseases or disorders associated with the need to promote the release of growth hormone or insulin, and use in detecting somatostatin receptors, e.g., radioimaging.

Other features and advantages of the present invention will be apparent from the detailed description and from the claims.

Detailed Description of the Invention

It is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and

not limitative of the remainder of the disclosure in any way whatsoever.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents, and other references mentioned herein are incorporated by reference.

Synthesis

The synthesis of short peptides is well examined in the peptide art. See e.g., Stewart, et al., Solid Phase Peptide Synthesis (Pierce Chemical Co., 2d ed., 1984). The following describes the synthesis of D-β-Nal-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2 and D-β-Nal-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2. Other peptides of the invention can be prepared in an analogous manner by a person of ordinary skill in the art.

(a) Synthesis of H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2.

1) Boc-β-naphthylalanine-S-methylbenzyl-D-cysteine-3-pyridyl-2-alanine-D-tryptophan-N^e-benzyloxycarbonyl-lysine-valine-S-methylbenzyl-cysteine-β-naphthylalanine-benzhydrylamine resin.

Benzhhydrylamine-polystyrene resin (Advanced ChemTech, Inc., Louisville, KY) (1.2 g; 0.5 mmole) in the chloride ion form was placed in the reaction vessel of an Advanced ChemTech™ peptide synthesizer programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid in methylene chloride (2 times for 1 and 25 min each); (c) methylene chloride; (d) ethanol; (e) methylene chloride; and (f) 10% triethylamine in chloroform.

The neutralized resin was stirred with Boc-0-β-naphthylalanine and diisopropylcarbodiimide (1.5 mmole each) in methylene chloride for 1 hr, and the resulting

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amino acid resin was then cycled through steps (a) to (f) in the above wash program. The following amino acids (1.5 mmole) were then coupled successively by the same procedure: Boc-S-methylbenzyl-Cys, Boc-Val, Boc-N^{ϵ}-benzyloxycarbonyl-lysine, Boc-D-Trp, Boc-Pal, and Boc-S-methylbenzyl-D-Cys and Boc-β-Nal. After washing and drying, the completed resin weighed 2.0 g.

2) β-naphthylalanine-c[D-cysteine-3-pyridyl-2-alanine-D-tryptophan:lysine-valine-cysteine]-β-naphthylalanine-NH_2

The completed resin described in (1) (1.0 g, 0.25 mmole) was mixed with anisole (5 ml), dithiothreitol (100 mg), and anhydrous hydrogen fluoride (35 ml) at O°C and stirred for 45 min. Excess hydrogen fluoride was evaporated rapidly under a stream of dry nitrogen, and the free peptide is precipitated and washed with ether. The crude peptide was then dissolved in 500 ml of 90% acetic acid to which was added a concentrated solution of I_2/MeOH until a permanent brown color is observed. Excess I_2 is removed by addition of ascorbic acid and the solution evaporated to a small volume which was applied to a column (2.5 x 90 cm) of Sephadex™ G-25, which was eluted with 50% AcOH. Fractions containing a major component by ultraviolet (UV) absorption and thin layer chromatography were then pooled, evaporated to a small volume, and applied to a column (1.5 x 70 cm) of Vydac™ octadecylsilane silica (10 - 15 μm). This was eluted with a linear gradient of acetonitrile in 0.1% trifluoroacetic acid in water. Fractions were examined by thin layer chromatography (TLC) and analytical high performance liquid chromatography (HPLC) and pooled to give maximum purity. Repeated lyophilization of the solution from water gave the desired product as a white, fluffy powder. The product was found to be homogeneous by HPLC and TLC. Amino acid analysis of an acid hydrolysate and matrix-assisted laser desorption (MALD) mass spectroscopy confirmed the composition of the

octapeptide.

(b) Synthesis of H_2-D-β-Nal-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2

1) Boc-β-D-naphthylalanine-D-4-chlorophenylalanine-O-dichlorobenzyl-tyrosine-D-tryptophan-N^e-benzyloxycarbonyl-lysine-valine-S-phenylalanine-O-benzyl-threonine-benzhydrylamine resin

Benzhydrylamine-polystyrene resin (Advanced ChemTech™, Inc.) (1.2 g, 0.5 mmole) in the chloride ion form was placed in the reaction vessel of an Advanced ChemTech peptide synthesizer programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid in methylene chloride (2 times for 1 and 25 min each); (c) methylene chloride; (d) ethanol; (e) methylene chloride; and (f) 10% triethylamine in chloroform.

The neutralized resin was stirred with Boc-O-benzylthreonine and diisopropylcarbodiimide (1.5 mmole each) in methylene chloride for 1 hr and the resulting amino acid resin was cycled through steps (a) to (f) in the above wash program. The following amino acids (1.5 mmole) were then coupled successively by the same procedure: Boc-phenylalanine, Boc-Val, Boc-N^e-benzyloxycarbonyl-lysine, Boc-D-Trp, Boc-O-dichlorobenzyl-Tyr, and Boc-D-4-chlorophenylalanine, and Boc-β-D-Nal. After washing and drying, the completed resin weighed 2.1 g.

2) β-D-naphthylalanine-D-4-chlorophenylalanine-tyrosine-D-tryptophan-lysine-valine-phenylalaninethreonine-NH_2

The peptide resin from (1) was subjected to HF cleavage as described above. Column purification as described yielded the desired compound as a white, fluffy powder (170 mg) which is found to be homogeneous by HPLC and TLC. Amino acid analysis of an acid hydrolysate and

MALD mass spectroscopy confirms the composition of the peptide.

Peptides containing C-terminal substituted amides can be made by solid phase methods by displacing the appropriate peptide off the solid phase with the corresponding amine. Alternatively, these analogs may be synthesized by solutionphase peptide synthesis methods in which the growing peptide chain is maintained in solution in an organic solvent during synthesis and assembled by iterative coupling/deprotection cycles. Final removal of the side chain protecting groups yields the desired peptide after appropriate purification. Peptides containing N-terminal substitutions (e.g., where R_1 is E, CO, or E_1SO_2 (where E_1 is heterocycle lower alkyl) substituted with hydroxy lower alkyl and R_2 is H such as 4-(2- hydroxyethyl)-1-piperazinylacetyl or 4-(2-hydroxyethyl)-1-piperdineethanesulfonyl) can be synthesized as described in PCT Application No. WO 95/04752.

Bioassay on the In Vitro Release of Growth Hormone

(a) Rat Pituitary Cell Dispersion

Pituitaries from adult Charles River CD male rats (Wilmington, MA) housed under controlled conditions were dispersed and cultured using aseptic technique by modification of previously described methods (Hoefer, M.T., et al., Mol. Cell. Endocrinol. 35:229 (1984); Ben-Jonathan, N., et al., Methods Enzymol. 103:249 (1983); and Heiman, M.L., et al., Endocrinology 116:410 (1985)). Pituitaries were removed from sacrificed rats, sectioned, and then placed into a siliconized, liquid scintillation vial containing 2 ml 0.2% trypsin (Worthington Biochemicals, Freehold, NJ) in sterilefiltered Krebs-Ringer bicarbonate buffer supplemented with 1% bovine serum albumin, 14 mM glucose, modified Eagle medium (MEM) vitamin solution, and MEM amino acids (Gibco Laboratories, Grand Island, NY) (KRBGA). All glassware was siliconized as

described by Sayers, et al., Endocrinology 88:1063 (1971). The fragments were incubated in a water bath for 35 min at 37°C with agitation. The vial contents then were poured into a scintillation vial containing 2 ml 0.1% DNase (Sigma Chemical Co., St. Louis, MO) in KRBGA and incubated for 2 min at 37°C with agitation. After incubation, the tissue was decanted into a 15 ml centrifuge tube and allowed to settle. Medium was discarded, and pituitary sections were washed 3 times with 1 ml fresh KRBGA. The cells were then dispersed in 2 ml 0.05% LBI (lima bean trypsin inhibitor, Worthington Biochemicals) by gently drawing the fragments into and expelling them out of a siliconized, fire polished Pasteur pipette. Dispersed cells were then filtered through a 630 μm diameter Nylon mesh (Tetko, Elmsford, NY) into a fresh 15 ml centrifuge tube. An additional 2 ml of 0.05% LBI solution was used to rinse the first tube and was transferred to the second tube with filtering.

(b) Cell culture

The dispersed cells were then further diluted with approximately 15 ml sterile-filtered Dulbeccol's modified Eagle medium (GIBCO), which was supplemented with 2.5% fetal calf serum (GIBCO), 3% horse serum (GIBCO), 10% fresh rat serum (stored on ice for no longer than 1 hr) from the pituitary donors, 1% MEM non-essential amino acids (GIBCO), and gentamycin (10 ng/ml; Sigma) and nystatin (10,000 U/ml; GIBCO). The cells were poured into a 50 ml round-bottomed glass extraction flask with a large diameter opening and then randomly plated at a density of approximately 200,000 cells per well (Co-star cluster 24; Rochester Scientific Co., Rochester, NY). The plated cells were maintained in the above Dulbeccols medium in a humidified atmosphere of 95% air and 5% CO_2 at 37°C for 4-5 days.

(c) Experimental incubation and IC_{50} determination

In preparation for a hormone challenge, the cells were

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washed 3 times with medium 199 (GIBCO) to remove old medium and floating cells. Each treatment well contained a total volume of 1 ml medium 199 containing 1% BSA (fraction V; Sigma) with treatments as described below. Each antagonist candidate was tested using a single 24-well cell culture plate. Each treatment was performed in triplicate. Each plate contained 8 treatment groups: one 1 nM growth hormone releasing factor (GRF) (1-29)NH_2-stimulated control group; one 1 nM somatostatin-inhibited control group in the presence of 1 nM GRF(1-29)NH_2; and 6 doses of a given antagonist in the presence of both 1 nM SRIF and 1 nM GRF per plate. After 3 hrs at 37°C in a air/carbon dioxide atmosphere (95/5%), the medium was removed and stored at -20°C until radioimmunoassayed for growth hormone content. IC_{50}'s of each antagonist versus 1 nm @ SRIF were calculated using a computer program (*SigmaPlot*, Jandel Scientific, San Rafael, CA) with the maximum response constrained to the value of the 1 nm GRF(1-29)NH_2-stimulated control. These IC_{50}'s are presented in Table I.

TABLE I

ANALOG NO.	IC_{50} (μM)	ANALOG NO.	IC_{50} (μM)
1	3.03	30	0.0065
2	0.04	31	0.0038
3	0.01	32	0.012
4	0.03	33	1.50
5	0.06	34	0.42
6	0.9	35	0.052
7	0.071	36	1.03
8	3.96	37	0.78
9	1.36	38	0.11
10	0.62	39	0.034
11	0.72	40	0.11
12	0.056	41	0.21
13	0.11	42	0.044
14	0.11	43	0.00082
15	0.14	44	0.021
16	0.82	45	0.13
17	1	46	0.02
18	0.38	47	0.053
19	0.11	48	0.050
20	0.12	49	0.23
21	0.97	50	0.0011
22	0.066	51	0.012
23	0.91	52	0.0026
24	0.068	53	0.0029
25	0.28	54	0.029
26	0.38	55	0.0026
27	0.041	56	0.0018
28	0.10	57	0.0059
29	0.0084		

Other

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the claims.

What is claimed is:

1. A compound of the formula:

$$R_1 \quad A^1\text{-}A^2\text{-}A^3\text{-}A^4\text{-Lys-}A^6\text{-}A^7\text{-}A^8\text{-}R_3,$$
$$R_2$$

wherein

A^1 is a D- or L-isomer of an aromatic amino acid, or is deleted;

A^2 is a D-isomer selected from the group consisting of of Cys, Pen, an aromatic amino acid, or an aliphatic amino acid;

A^3 is an aromatic amino acid;

A^4 is Trp or D-Trp;

A^6 is Thr, Thr(Bzl), Gly, Ser, an Eaa, or an aliphatic amino acid;

A^7 is Cys, Pen, or an aromatic or an aliphatic amino acid;

A^8 is a D- or L-isomer selected from the group consisting of Thr, Ser, an aromatic amino acid, or an aliphatic amino acid;

each of R_1 and R_2, is, independently, H or substituted or unsubstituted lower alkyl, aryl, aryl lower alkyl, heterocycle, heterocycle lower alkyl, E_1SO_2 or E_1CO (where E_1, is aryl, aryl lower alkyl, heterocycle, or heterocycle lower alkyl), where said substituent is halo, lower alkyl, hydroxy, halo lower alkyl, or hydroxy lower alkyl; and

R_3 is OH, NH_2, C_{1-12} alkoxy, or NH-Y-CH_2-Z, wherein Y is a C_{1-12} hydrocarbon moiety and Z is H, OH, CO_2H, or $CONH_2$, or R_3, together with the carbonyl group of A^8 attached thereto, are reduced to form H, lower alkyl, or hydroxy lower alkyl; provided if A^2 is D-Cys or D-Pen, and A^7 is Cys or Pen, then a disulfide bond links the sidechains of A^2 and A^7, and if A^1 is D-Phe or p-NO_2-Phe; A^2 is D-Cys; A^3 is Phe or Tyr; A^6

is Thr or Val; and A^7 is Cys; then A^8 is β-Nal.

2. A compound of claim 1, wherein A^2 is D-Cys, A^7 is Cys, and A^4 is D-Trp.

3. A compound of claim 2, wherein A^1 is an L-aromatic amino acid.

4. A compound of claim 3, wherein A^1 and A^3, independently, is β-Nal, o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal.

5. A compound of claim 4, wherein A^1 is β-Nal, Npa, Igl, Phe, p-F-Phe, Trp, p-Cl-Phe, or p-CN-Phe; A^3 is Tyr, Tyr(I), or Pal; A^6 is Val, Tle, Nle, Ile, or Leu; A^8 is p-F-Phe, β-Nal, Tyr, Dip, p-Cl-Phe, Igl, or p-CN-Phe; R_1 is H, CH_3CO, 4- (2-hydroxyethyl) -1-piperazinylacetyl, or 4-(2-hydroxyethyl)-1-piperizineethanesulfonyl; R_2 is H; and R_3 is NH_2.

6. A compound of claim 5, wherein A^3 is Pal.

7. A compound of claim 4 of the formula:

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H) (CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2 (V);

(H)-(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)-(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H) (CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)-(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)-(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H) (CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H) (4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H) (4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H) (CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H) (4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H) (4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-O-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H) (CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H) (4-(2-hydroxyethyl)-1-piperazinylacetyl)-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H) (4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H) (CH_3CO)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H) (4-(2-hydroxyethyl)-1-piperazinylacetyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H) (4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(CH_3CO)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)

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Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(CH_3CO)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal- NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(CH_3CO)-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Abu-Cys-β-Nal-NH_2; * and dm.3/4 isomer

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

H_2-Phe-D-Pen-Tyr-D-Trp-Lys-Val-Pen-β-Nal-NH_2; or

H_2,-Phe-D-Pen-Pal-D-Trp-Lys-Thr-Pen-Thr-NH_2;

H_2-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-Dip-NH_2;

H_2-F_5-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-F_5-Phe-NH_2;

H_2-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

H_2-m-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-m-F-Phe-NH_2;

H_2-o-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-o-F-Phe-NH_2;

H_2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-p-F-Phe-NH_2;

H_2-F_5-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-F_5-Phe-NH_2;

H_2-F_5-Phe-D-Cys-2-Pal-D-Trp-Lys-Val-Cys-F_5-Phe-NH_2;

H_2-β-Nal-D-Cys-His-D-Trp-Lys-Val-Cys-D-Dip-NH_2;

H_2-Dip-D-Cys-His-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-Dip-D-Cys-His-D-Trp-Lys-Val-Cys-Dip-NH_2;
H_2-β-Nal-D-Cys-His-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-Trp-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-p-F-Phe-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;
H_2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Nle-Cys-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Ile-Cys-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Gly-Cys-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Ala-Cys-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Leu-Cys-β-Nal-NH_2;
H_2-Bip-D-Cys-Tyr-D-Trp-Lys-Ile-Cys-Bip-NH_2;
H_2-p-F-Phe-D-Cys-His-D-Trp Lys-Val-Cys-p-F-Phe-NH_2;
H_2-Npa-D-Cys-Pal-D-Trp-Lys-Val-Cys-Tyr-NH_2;
H_2-m-F-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-m-F-Phe-NH_2;
H_2-o-F-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-o-F-Phe-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Dip-NH_2;
H_2-Cpa-D-Cys-Pal-D-Trp-Lys-Val-Cys-Cpa-NH_2;
H_2-Igl-D-Cys-Pal-D-Trp-Lys-Val-Cys-Igl-NH_2;
H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-Dip-NH_2;
H_2-β-Nal-D-Cys-3-I-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-p-CN-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-p-CN-Phe-NH_2;
H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-Dip-NH_2;
H_2-β-Nal-D-Cys-Bta-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;
H_2-Bpa-D-Cys-Pal-D-Trp-Lys-Val-Cys-Bpa-NH_2;
H_2-Iph-D-Cys-Pal-D-Trp-Lys-Val-Cys-Iph-NH_2;
H_2-Trp-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;
H_2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;*
H_2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;
H_2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-p-Cl-Phe-NH_2;
H_2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Cha-Cys-p-Cl-Phe-NH_2;
H_2-p-Cl-Phe-D-Cys-Tr(I)-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH_2;

H_2-p-Cl-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-p-Cl-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;
H_2-p-F-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-p-F-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;
(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;
H_2-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;
(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2;
H_2-p-N02-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-Nal-NH_2;
(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-β-Nal-NH_2;
(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Tyr-NH_2;
H_2-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-β-Nal-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-β-Nal-NH_2; or
(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-NH_2; or a pharmaceutically acceptable salt thereof.

8. A compound of claim 2, wherein A^1 is a D-aromatic amino acid.

9. A compound of claim 8, wherein A^1 is D-β-Nal, D-o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), Dm-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-F_5-Phe, D-Trp, D-Dip, D-2-Pal, D-Tyr(Bzl), D-His, D-Igl, DTyr(I), D-Bta, D-Bip, D-Npa, or D-Pal; A^3 is β-Nal, o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2),

p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal.

10. A compound of claim 9, wherein A^1 is D-β-Nal, D-Npa, D-Igl, D-Phe, D-p-F-Phe, D-Trp, D-p-Cl-Phe, or D-p-CN-Phe; A^3 is Tyr, Tyr(I), or Pal; A^6 is Val, Tle, Nle, Ile, or Leu; A^8 is p-F-Phe, β-Nal, Tyr, Dip, p-Cl-Phe, Igl, or p-CN-Phe; R_1 is H, CH_3CO, 4-(2-hydroxyethyl)-1-piperazinylacetyl, or 4-(2-hydroxyethyl)-1-piperizineethanesulfonyl; R_2 is H; and R_3 is NH_2.

11. A compound of claim 10, wherein A^3 is Pal.

12. A compound of claim 8, of the formula:
H_2-D-Phe-D-Pen-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;
H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;
H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;
H_2-D-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;
H_2-D-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;
H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;
H_2-D-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-β-Nal-NH_2;
H_2-D-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-p-F-Phe-NH_2;
H_2-D-Bip-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-D-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;
H_2-D-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-β-Nal-NH_2;
H_2-D-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-p-Cl-Phe-NH_2;
p-NO_2-D-Phe-D-Cys-Pal-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-

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NH_2;

p-NO_2-D-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Val-Cys-Tyr(Bzl)-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-D-Phe-D-Cys-Pal-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-NH_2; or

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO_2-D-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Val-Cys-Tyr(Bzl)-NH_2; or a pharmaceutically acceptable salt thereof.

13. A compound of claim 2, wherein A^1 is deleted, R^1 is substituted or unsubstituted E_1CO, and R_2 is H.

14. A compound of claim 13, wherein R_1 is substituted or unsubstituted E_1CO (where E_1 is phenyl, β-naphthylmethyl, β-pyridinylmethyl, or 3-indolylmethyl); A^3 is β-Nal, o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal.

15. A compound of claim 14, wherein R_1 is E_1CO (where E_1 is 4-hydroxy-phenyl, β-naphthylmethyl, or phenyl); A^3 is Tyr, Tyr (I), or Pal; A^6 is Val, Tle, Nle, Ile, or Leu; A_8 is p-F-Phe, β-Nal, Tyr, Dip, p-Cl-Phe, Igl, or p-CN-Phe; R_3 is NH_2.

16. A compound of claim 15, wherein A^3 is Pal.

17. A compound of claim 14, of the formula

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(H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2 ;

(H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-β-Nal-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH_2;

(H)(3-[p-hydroxyphenyl])-D-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2;

(H)(3-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-

BNSDOCID: <WO___9824807A2_I_>

β-Nal-NH_2;

(H)(3-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2;

(H)(3-phenylylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH_2; or

(H)(3-phenylylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH_2; or

a pharmaceutically acceptable salt thereof.

18. A compound of claim 2, wherein R_3, together with the carbonyl group of A^8 attached thereto, are reduced to form H, lower alkyl, or hydroxy lower alkyl.

19. A compound of claim 18, wherein A^1 is the D- or L-isomer of β-Nal, o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), -p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^3 is β-Nal, o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal.

20. A compound of claim 19, wherein A^1 is the D- or L-isomer of β-Nal, Phe, p-F-Phe, Trp, p-Cl-Phe, or p-CN-Phe; A^3 is Tyr, Tyr (I), or Pal; A^6 is Val, Tle, Nle, Ile, or Leu; A^8 is p-F-Phe, β-Nal, Tyr, Dip, p-Cl-Phe, Igl, or p-CN-

Phe; R_1 is H, CH_3CO, 4-(2-hydroxyethyl)-1-piperazinylacetyl, or 4-(2-hydroxyethyl)-1-piperizineethanesulfonyl; R_2 is H, and R_3, together with the carboxy group of A^8 attached thereto, are reduced to form H or CH_3OH.

21. A compound of claim 20, wherein A^3 is Pal.

22. A compound of claim 19, of the formula:

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2,-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

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(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H(CH_3CO)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H) (CH_3CO) Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R, 3R- (2-hydroxymethyl)-3-hydroxy)propylamide;

(H) (4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H) (4-(2-hydroxyethyl)-1-piperizineethanesulfonyl) Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H) (CH_3CO)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H) (4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H) (4-(2-hydroxyethyl)-1-piperizineethanesulfonyl) Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H) (CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H) (4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H) (4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H) (CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H) (4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H) (4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)

ethylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R- (2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(CH_3CO)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R- (2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(CH_3CO)Phe-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(CH_3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(CH_3CO)Phe-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R-(2-naphthyl)ethylamide;

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R-(2-naphthyl)ethylamide;

H_2-β-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; or

H_2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; or a pharmaceutically-acceptable salt thereof.

23. A compound of claim 1, wherein A_2 is a D-aromatic amino acid or a D-aliphatic amino acid, A_7 is an aromatic amino acid or an aliphatic amino acid, and A_4 is D-trp.

24. A compound of claim 23, wherein A_1 is an L- amino acid and A_2 is a D-aromatic amino acid.

25. A compound of claim 24, wherein A_1, A_3, and A_7 independently, is β-Nal, o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN or NO_2), p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, Tyr(Bzl), His, Igl, Tyr(I), Bta, Bip, Npa, or Pal; A^2 is D-

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β-Nal, D-o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-F_5-Phe, D-Trp, D-Dip, D-2-Pal, D-Tyr(Bzl), D-His, D-Igl, D-Tyr(I), DBta, D-Bip, D-Npa, or D-Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr (Bzl), or β-Nal.

26. A compound of claim 25, wherein A^1 is β-Nal or Phe, A^2 is D-Cpa or D-Phe; A^3 is Phe or Tyr; A^6 is Abu, Thr, or Val; A^7 is Phe; and A^8 is Thr; R_1 is H, CH_3CO, 4-(2-hydroxyethyl)-1-piperazinylacetyl, or 4-(2-hydroxyethyl)-1-piperizineethanesulfonyl; R_2 is H; and R_3 is NH_2.

27. A compound of claim 25 of the formula:

H_2-Phe-D-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H_2-Phe-D-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-Phe-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(CH_3CO)-β- Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-β-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(CH_3CO)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

BNSDOCID <WO 9824807A2 >

(H)(CH_3CO)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H_2-β-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(CH_3CO)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H_2-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2;

(H)(CH_3CO)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2;

(H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2; or

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2;

H_2-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2-; or

H_2-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2; or a pharmaceutically acceptable salt thereof.

28. A compound of claim 23, wherein A^1 is a D-amino acid and A^2 is a D-aromatic amino acid.

29. A compound of claim 28, wherein A^1 and A^2, independently, is D-β-Nal, D-o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), D-F_5-Phe, D-Trp, D-Dip, D-2-Pal, D-Tyr(Bzl), D-His, D-Igl, D-Tyr(I), D-Bta, D-Bip, D-Npa, or DPal; A^3 and A^7, independently, is β-Nal, o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), p-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH, CH_3, halo, OCH_3, NH_2, CN, or NO_2), F_5-Phe, Trp, Dip, 2-Pal, His, Igl, Tyr(I), Bta, Bip, Npa, Tyr(Bzl),

BNSDOCID: <WO___9824807A2_I_>

or Pal; A^6 is Thr, Ser, Tle, Thr(Bzl), Abu, Ala, Ile, Leu, Gly, Nle, β-Ala, Gaba, or Val; and A^8 is the D- or L-isomer of Thr, Dip, F_5-Phe, p-XPhe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), o-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), m-X-Phe (where X is H, OH CH_3, halo, OCH_3, NH_2, CN, or NO_2), Igl, Tyr(Bzl), or β-Nal.

30. A compound of claim 29, wherein A^1 is D-β-Nal or D-Phe; A^2 is D-Cpa or D-Phe; A^3 is Phe or Tyr; A^6 is Thr or Val; A^7 is Phe; and A^8 is Thr; R_1 is H, CH_3CO, 4-(2-hydroxyethyl)-1-piperazinylacetyl, or 4-(2-hydroxyethyl)-1-piperizineethanesulfonyl; R_2 is H; and R_3 is NH_2.

31. A compound of claim 29 of the formula:

H_2-D-β-Nal-D-Cpa-Phe-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-D-β-Nal-D-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2;

H_2-D-Phe-D-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2;

H_2-D-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2; or

H_2-D-β-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-β-Nal-NH_2; or

a pharmaceutically acceptable salt thereof.

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 7/00

A2

(11) International Publication Number: WO 98/24807

(43) International Publication Date: 11 June 1998 (11.06.98)

(21) International Application Number: PCT/US97/22251

(22) International Filing Date: 4 December 1997 (04.12.97)

(30) Priority Data:

60/032,358	4 December 1996 (04.12.96)	US
08/760,672	4 December 1996 (04.12.96)	US
08/855,204	13 May 1997 (13.05.97)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application

US 08/855,204 (CIP)
Filed on 13 May 1997 (13.05.97)

(71) Applicants *(for all designated States except US)*: BIOMEASURE INCORPORATED [US/US]; 27 Maple Street, Milford, MA 01757-3650 (US). THE ADMINISTRATION OF THE TULANE EDUCATIONAL FUND [US/US]; 1430 Tulane Avenue, New Orleans, LA 70112 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MORGAN, Barry [GB/US]; 237 Prospect Street, Franklin, MA 02038 (US). MURPHY, William [US/US]; 1242 St. Christopher Drive, Slidell, LA 70460 (US). COY, David, H. [US/US]; 1529 Fourth Street, New Orleans, LA 70130 (US).

(74) Agent: TSAO, Y., Rocky; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: SOMATOSTATIN ANTAGONISTS

(57) Abstract

The invention features somatostatin antagonists having a D–amino acid at the second residue.

*(Referred to in PCT Gazette No. 38/1998, Section II)

BNSDOCID: <WO___9824807A2_IA>

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BNSDOCID: WO 9824907A2 IA

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 14/655, 7/06

A3

(11) International Publication Number: WO 98/24807

(43) International Publication Date: 11 June 1998 (11.06.98)

(21) International Application Number: PCT/US97/22251

(22) International Filing Date: 4 December 1997 (04.12.97)

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(74) Agent: TSAO, Y., Rocky; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110 (US).

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Published
With international search report.

(88) Date of publication of the international search report: 15 October 1998 (15.10.98)

(54) Title: SOMATOSTATIN ANTAGONISTS

(57) Abstract

The invention features somatostatin antagonists having a D-amino acid at the second residue.

*(Referred to in PCT Gazette No. 38/1998, Section II)

BNSDOCID: <WO___9824807A3_I_>

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/22251

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/655 C07K7/06

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 4 853 371 A (COY DAVID H ET AL) 1 August 1989 see column 3, line 60-61; claims 1-11	1-22
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 July 1998	06/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kronester-Frei, A

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BNSDOCID: <WO___9824807A3_I_>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/22251

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PCT/US 97/22251

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